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### Effects of Hypoxia and Hyperoxia of Short Duration on the Pulmonary Circulation of Highlanders (HL) and Lowlanders (LL) Living at 3,750 m

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It is now very well known that pulmonary artery pressures (PAP) are increased permanently in people born and living at altitudes over 3,000 m [12, 17]. The same degree of pulmonary artery hypertension (PAH) also appears from the first day of acclimatization, in people coming from sea level to high altitude [13].

The pulmonary arteriolar vasoconstriction is the mechanism usually used to explain the increase in PAP during hypoxic conditions. Since the first studies made by BEYNE [5] in 1942 and VON EULER and LILJESTRAND [8] many further studies have been made and the results for the most part have been contradictory. According to MCGREGOR [15], the reason for these contradictions in data is related to variations in blood pH. It has been found that acidosis is, in general, a potentiating factor of vasoconstriction. Alkalosis, on the other hand, tends to diminish this response and produce the opposite effect [20].  $PCO_2$  tension in arterial blood must also be taken into account when considering the effects of hypoxia [7].

The second mechanism that is given consideration in the explanation of increased PAP in highlanders is that there are modifications in the structure of the pulmonary arteries at their origin [11] and at their termination. Specifically, it has been found that there is a relative increase in the 'tunica muscularis' layer of the pulmonary arteries [1].

The study has been done to quantify to what extent the two aforementioned mechanisms, functional and structural, maintain the increase in PAP in people who dwell in high altitudes.

## *Methodology*

We chose a method allowing a rapid variation in the partial pressure of oxygen ( $PO_2$ ) while limiting the secondary effects of the prolonged inhalation of oxygen. It is known that the prolonged inhalation of pure  $O_2$  produces variations in blood  $PCO_2$  and pH that may interfere with pulmonary circulation. The method of short hyperoxia and hypoxia used for many years by the respiratory physiologists [6] seemed very appropriate for the study of pulmonary vasomotricity which is produced only by variations of  $PO_2$ .

Two tidal volumes of pure oxygen ( $O_2$  test) or pure nitrogen ( $N_2$  test) were inhaled by the subject lying in a supine position, connected by a mouthpiece to a valve. This valve (of small dead space) communicates on its inspiratory side with a three-way stopcock. The mean pulmonary pressure ( $\overline{PPA}$ ), measured with a floating catheter set in the pulmonary artery trunk, was registered before, during and 2 min after the gas inhalation test. The heart rate (HR) was registered at the same time and measured by counting the number of cardiac cycles per 10-sec interval. No premedication was given. The test was repeated every 3 min. This period of time was enough for the variables being studied to return to the baseline. Six tests were performed on every subject. The subjects refused to let their blood be sampled, so that it was not possible to measure the cardiac output (CO), blood  $PO_2$ ,  $PCO_2$  and PH.

The studies were completed in La Paz (3,750 m;  $\overline{PB} = 495$  mm Hg) on two groups of soldiers from the same ethnic group (Aymara) of the same age (19–21 years old), and who were considered normal after a routine health checkup: Eleven were born and have lived at an altitude below 500 m and then had come to La Paz 9 months before the study (LL group). 13 were born and lived at high altitude, (3,800 m) (HL group). A complementary study was done on 7 subjects from the HL group: i.e.  $O_2$  tests were performed while the subject inhaled a hypoxic gas for at least 30 min ( $FIO_2 = 0.168$ ).

## *Results*

It is noted that the mean PAP before stimulation was not significantly different between the two groups ( $0.30 < p < 0.50$ ):  $20.4 \pm 5.3$  mm Hg for the LL group;  $21.0 \pm 3.0$  mm Hg for the HL group.

### *A. Results of the $O_2$ Tests (fig. 1)*

In the two groups there is a significant ( $p < 0.01$ ) and rapid decrease of  $\overline{PPA}$  (at an average of 10 sec after the beginning of gas inhalation test). The amplitude of the change is maximal after 40 sec.

The decrease of  $\overline{PPA}$ , produced by the  $O_2$  tests is approximately two times larger in the LL group (decrease of 13.7%) than in the HL group (decrease of 6.2%;  $p < 0.001$ ).

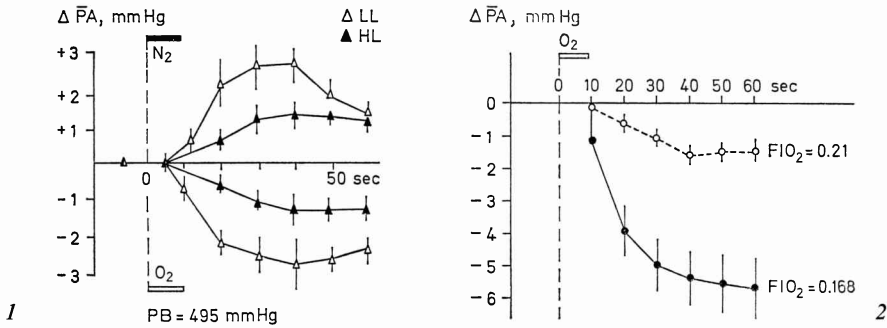


Fig. 1. Changes of the mean pulmonary artery pressure ( $\Delta\bar{P}A \pm SE$ ) observed in the O<sub>2</sub> and N<sub>2</sub> tests in 11 subjects born at low altitude and removed to 3,750 m (LL), and in 13 subjects born at high altitude (HL).

Fig. 2. Changes of the mean pulmonary artery pressure ( $\Delta\bar{P}A \pm SE$ ) observed in the O<sub>2</sub> tests in 7 highlanders inhaling ambient air (PIO<sub>2</sub> = 94 mm Hg) and hypoxic gas (PIO<sub>2</sub> = 75 mm Hg).

For the 7 subjects of the HL group having inhaled a previous gas mixture with 16.8% of O<sub>2</sub> the amplitude of the decrease of PPA after O<sub>2</sub> test is significantly increased ( $p < 0.005$ ) (fig. 2).

### B. Results of the N<sub>2</sub> Tests (fig. 1)

The increase of PPA, which is maximum after the 40th second following the gas inhalation test is significant in all tests ( $p < 0.01$ ). It is approximately two times larger in the LL group (increase of 13.9%) than in the HL group (increase of 6.7%) ( $p < 0.005$ ).

## Discussion

### A. Can Vasoconstriction of the Pulmonary Capillary Bed Be Considered as the Only Mechanism Responsible for the PAP Variations Induced by Brief Hypoxia and Hyperoxia, or Do Other Mechanisms such as Cardiac Output Variations Play a Role in PAP Variations?

It is noted that the variations in heart rate follow the variations in PAP (fig. 3). In hyperoxic conditions, heart rate falls 13.1% in the LL group and 6.8% in the HL group ( $p < 0.03$ ), but O<sub>2</sub> tests do not modify the amplitude of the HR response in the 7 HL subjects submitted

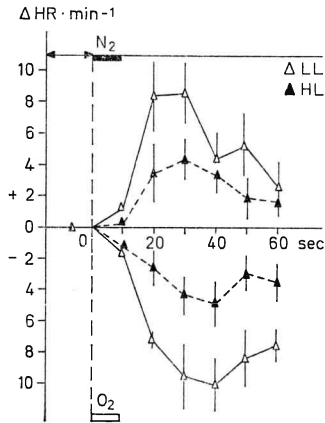


Fig. 3. Changes of heart rate ( $\Delta\text{HR} \pm \text{SE}$ ) observed at 3,750 m in the  $\text{O}_2$  and  $\text{N}_2$  tests in 11 subjects born at low altitude (LL) and in 13 subjects born at high altitude (HL).

to previous inhalation of hypoxic mixtures ( $p > 0.05$ ). In hypoxic conditions during the  $\text{N}_2$  test, HR increases 10.2% in the LL group and 7.0% in the HL group, but the difference is not statistically significant ( $p > 0.05$ ).

It was possible to separate the response of PAP to the  $\text{O}_2$  test from the response of HR in one lowlander subject and in one highlander subject by pharmacological isolation of the heart (fig. 4). This pharmacological isolation was obtained by an i.v. perfusion of propranolol over a period of 40 min at a dosage of 0.15 mg/kg; 3 mg of atropine sulfate was perfused at the same time. Satisfactory pharmacological isolation was verified by an i.v. injection of isoproterenol ( $4 \mu\text{g}/\text{min}$  over a period of 3 min) and the second series of tests was made only when no modification of HR was observed during the injection:

1. In the first case (LL) during  $\text{O}_2$  tests,  $\bar{\text{PAP}}$  diminished 15.6% before the pharmacological block and 13.0% after blockage. HR diminished 11.1% before blockage and increased 7.9% after blockage.

2. In the second case (HL)  $\bar{\text{PAP}}$  diminished 9.7% and HR diminished 8.3% before blockage and  $\bar{\text{PAP}}$  diminished 25% but HR did not change after blockage.

It seems certain that the PAP variations, independent of the occasional variations of HR, are not due to variations of cardiac output. Other investigators did not notice any correlation between the variations

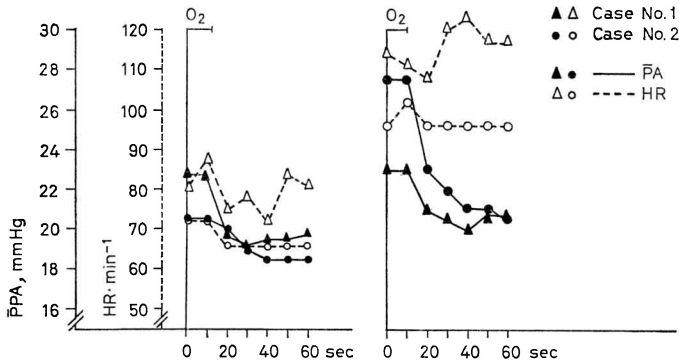


Fig. 4. Variations of the mean pulmonary artery pressure ( $\bar{P}_{PA}$ ) and of heart rate (HR) in two cases after inhalation of two tidal volumes of pure  $O_2$  ( $O_2$  test): *A* before pharmacological block of the heart; *B* after pharmacological block of the heart.

of pulmonary blood flow [2] or volume [10] and the variations of PAP during hypoxia.

It is then possible to conclude that the PAP variations, induced by brief hypoxia or hyperoxia (obtained by inhalation of two tidal volumes of pure  $N_2$  and pure  $O_2$ ), do correspond in reality to variations of pulmonary vasomotricity. The works published on this subject point to a localization of this vasomotricity in the more distal part of the arterial tree [9] more precisely at the intraalveolar precapillary level [3, 4].

#### *B. How Should the Difference between Highlanders and Lowlanders Be Interpreted?*

As in LL, the HL pulmonary vascular bed reacts to brief  $PO_2$  variations, but the range of the response curve is reduced in the HL with regards to the range of response of the lowlanders (fig. 1). The range can be increased by the inhalation of hypoxic mixtures (fig. 2). This decrease of pulmonary circulation sensitivity to  $PO_2$  variations is comparable to the blunting of the chemoreflex ventilatory sensitivity already described in HL [14, 16, 18].

Functional vasoconstriction seems secondary for the determination of PAP in the HL and structural modifications of the pulmonary artery is the determining factor. This certainly explains why moderate and progressive decrease of PAPs is observed in HL transferred to sea level.

In fact, two years are needed for PAP values of HL to become identical to those observed in people born and living at sea level. This period seems needed for the completion of the structural involution of the pulmonary vascular bed [19].

In the LL, vasoconstriction is the essential mechanism for maintaining the increased PAP at high altitude.

### *Summary*

We have done brief O<sub>2</sub> and N<sub>2</sub> inhalations in order to analyze the mechanism responsible for the pulmonary artery hypertension observed at high altitude in normal residents and newcomers. The reactivity of the pulmonary vascular bed is approximately two times less in highlanders.

We conclude that the functional vascular reactivity in lowlanders is the predominant factor while this reactivity is secondary in the highlanders. In the latter, the structural changes seem to be the principal factor.

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